Acute kidney injury and malignancy

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Onco-nephrology

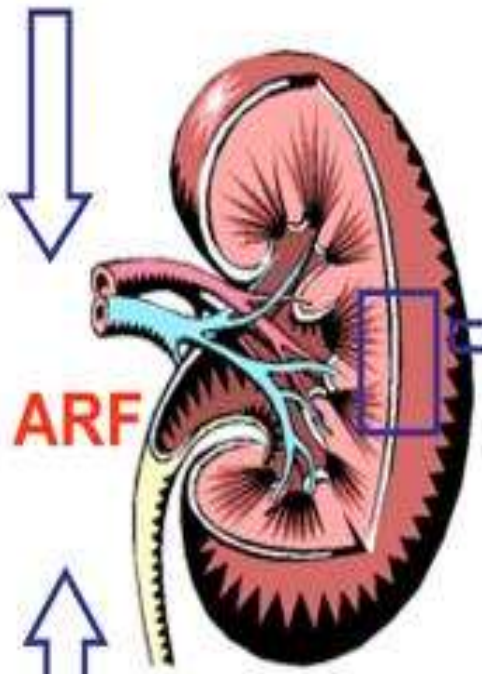
- AKI is an important complication of cancer and its treatment.

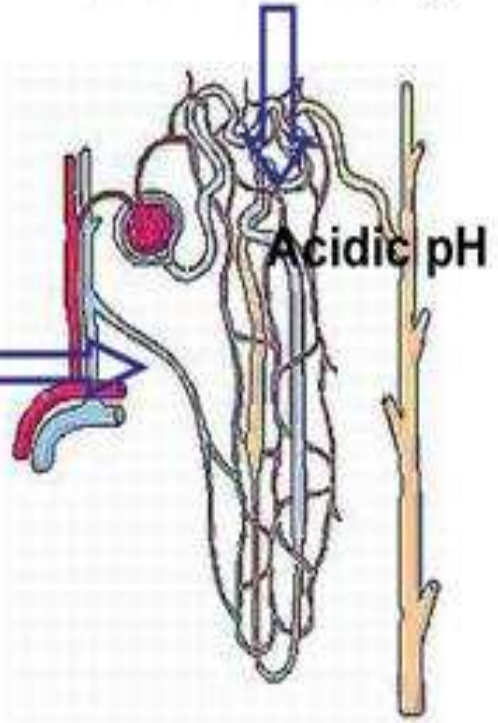
- In addition to hospital mortality, development of an ARF may preclude optimal cancer treatment by requiring a decrease in chemotherapy dosage or by contraindicating potentially curative treatment

Kidney obstruction or compression or renal vascular thrombosis in solid tumors

Cellular breakdown

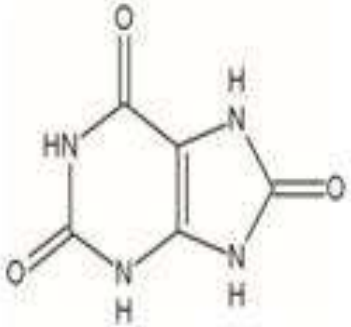
Uric acid crystals obstruct tubules and collecting ducts





Acidic pH

Uric acid and posphate



ARF

Chemotherapeutic, antibiotics, antiviral and antifungal drugs

Causes of acute renal failure in cancer patients

Pre-renal failure		Sepsis
		Extracellular dehydration (diarrhoea, mucitis, vomiting)
		Sinusoidal obstruction syndrome (formerly called hepatic veno-occlusive disease)
		Drugs (e.g., calcineurin inhibitors, ACE inhibitors, NSAIDs)
		Capillary-leak syndrome (IL2)
Intrinsic failure		
	Acute tubular necrosis	Ischaemia (shock, severe sepsis)
		Nephrotoxic agents (contrast agents, aminoglycosides, amphotericin, ifosfamide, cisplatin)
		Disseminated intravascular coagulation
		Intravascular haemolysis
	Acute interstitial nephritis	Immuno-allergic nephritis
		Pyelonephritis
		Cancer infiltration (e.g., lymphoma, metastasis)
		Nephrocalcinosis
	Vascular nephritis	Thrombotic microangiopathy
		Vascular obstruction
	Glomerulonephritis	Amyloidosis (AL, myeloma; AA, renal carcinoma or Hodgkin's disease)
		Immunotactoid glomerulopathy
		Membranous glomerulonephritis (pulmonary, breast or gastric carcinoma)
		IgA glomerulonephritis, focal glomerulosclerosis
Post-renal failure		Intra-renal obstruction (e.g., urate crystals, light chain, acyclovir, methotrexate)
		Extrarenal obstruction (retroperitonal fibrosis, ureteral or bladder outlet obstruction)

Prerenal Causes

- Volume depletion related to nausea, vomiting, or diarrhea as a toxicity of chemotherapy.

- Hypercalcemia related to direct renal vasoconstriction or natriuresis -volume depletion.

Postrenal Causes

- It is most common in cancers of the prostate, bladder, and kidney.

or

- Secondary to extrinsic compression of the urinary outflow tract from both primary and metastatic abdominal or pelvic malignancies.

(Pulmonary carcinoma is the most common solid tumor to metastasize to kidney).

Intrinsic Causes

- **Lymphomatous Infiltration of the Kidney.**
- **Cast Nephropathy.**
- **Tumor Lysis Syndrome.**

Lymphomatous Infiltration of the Kidney

- Although enlarged kidneys on imaging, AKI, and subclinical proteinuria are common findings, LIK is almost always diagnosed by renal biopsy .

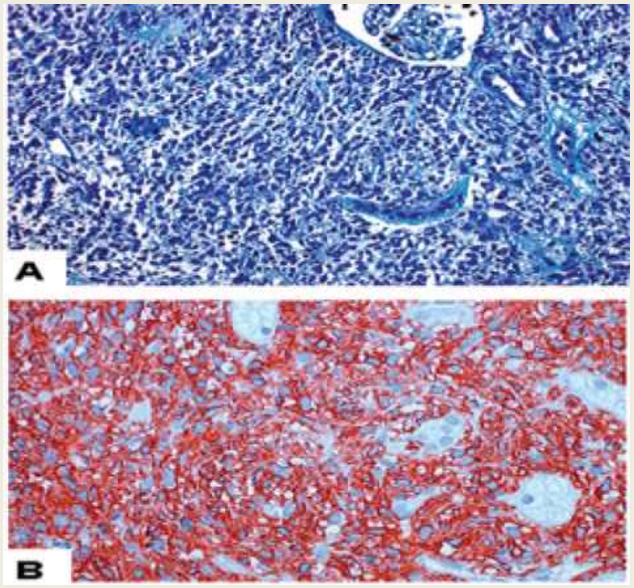


Table 4. **Summary of pathogenesis and treatment of acute renal failure due to lymphomatous infiltration of the kidneys**

Pathogenesis

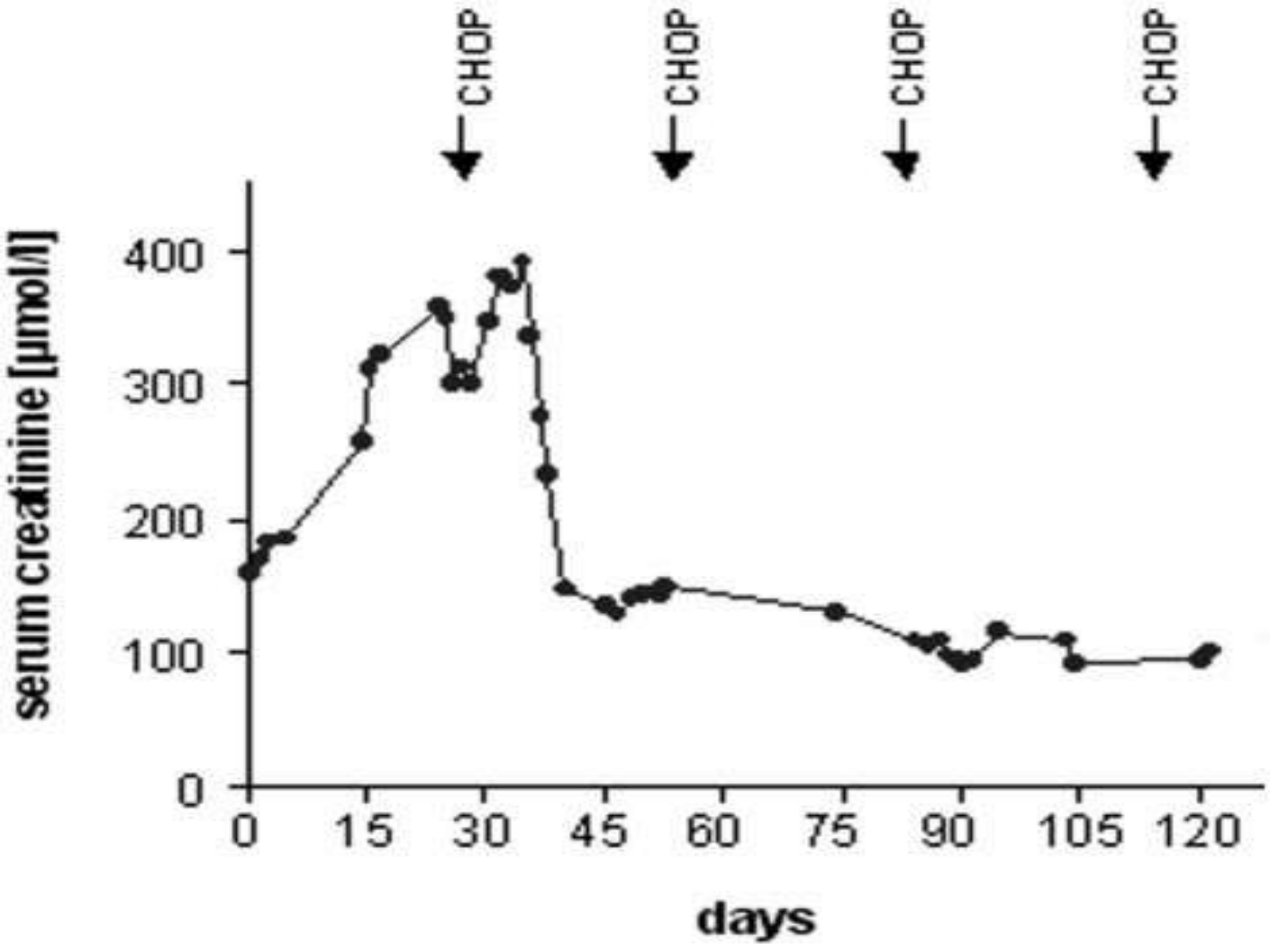
- the mechanism of acute renal failure due to lymphomatous infiltration of the kidneys is unknown
- infiltrate may compress tubules and cause intrarenal obstruction
- reversible acute tubular necrosis (ATN) has been described

Treatment

- rapid improvement with chemo- and/or radiotherapy is seen in most patients
- creatinine level usually returns to normal 1 to 4 wk after therapy is initiated
- decrease in kidney size parallels the improvement in renal function
- hydration and allopurinol are prescribed to protect against the effects of tumor lysis

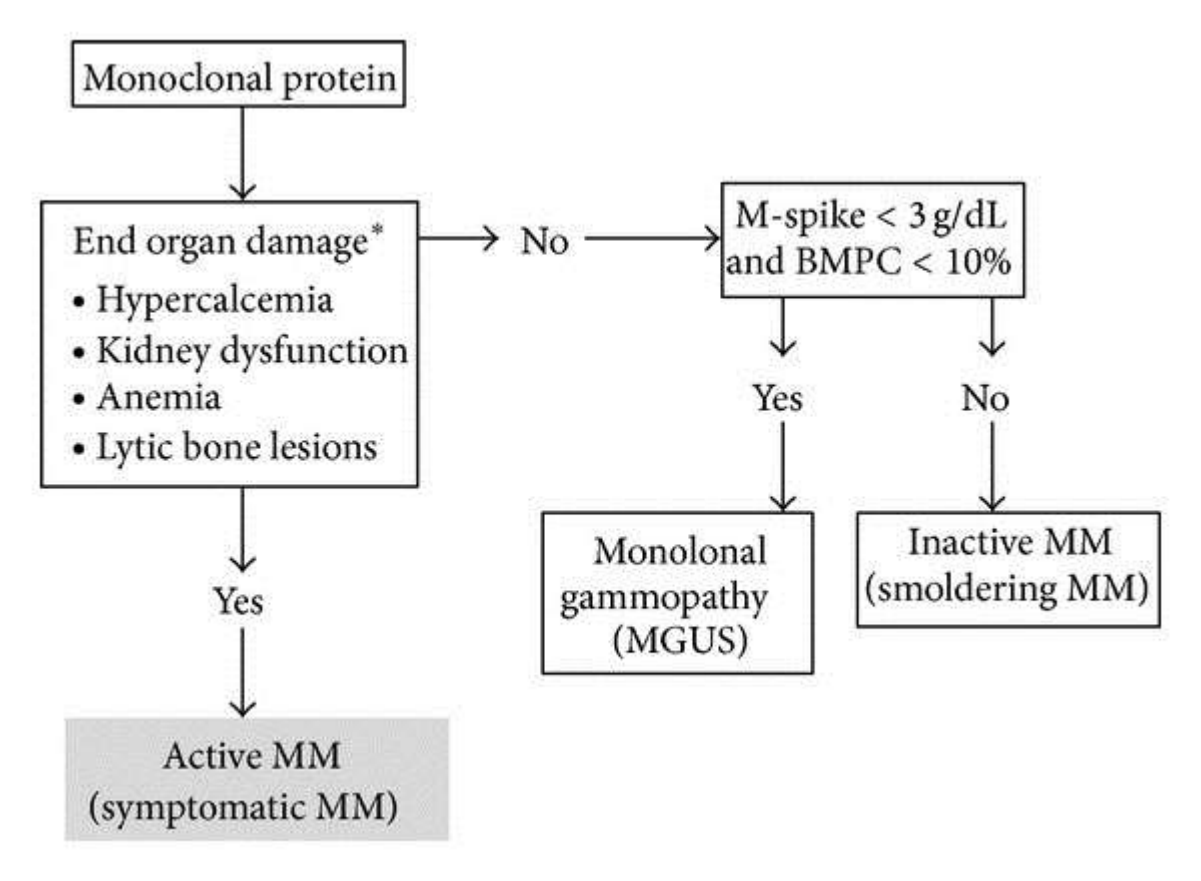
Prognosis

- patient survival is poor despite recovery of renal function


CHOP
CHOP
CHOP
CHOP
serum creatinine [µmol/l]
400
300
200
100
0
0
15
30
45
60
75
90
105
120
days

Cast Nephropathy

Multiple myeloma



Diagnostic Criteria for MM

- I = Plasmacytoma on tissue biopsy
- II = Bone marrow with greater than 30% plasma cells
- III = Monoclonal globulin spike on SPEP, with IgG peak > 3.5 g/dL or an IgA peak > 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) result >1 g/24 h
- a = Bone marrow with 10-30% plasma cells
- b = Monoclonal globulin spike present but less than category III
- c = Lytic bone lesions
- d = Residual IgM level < 50 mg/dL, IgA level < 100 mg/dL, or IgG level less than 600 mg/dL

- I plus b, c, or d
- II plus b, c, or d
- III plus a, c, or d
- a plus b plus c
- a plus b plus d

Initial therapy

- High-dose chemotherapy with autologous hematopoietic stem-cell transplantation has become the preferred treatment for patients under the age of 65. Prior to transplantation, these patients receive an initial course of induction chemotherapy. The most common induction regimens used are thalidomide–dexamethasone, bortezomib based regimens, and lenalidomide–dexamethasone .
- Autologous stem cell transplantation (ASCT) is not curative, but does prolong overall survival and complete remission. Allogeneic stem cell transplantation, has the potential for a cure, but is used in a very small percentage of patients and in the relapsed setting, not as part of initial treatment.

Maintenance therapy

- Sometimes after the initial treatment an ongoing maintenance therapy is offered. "In younger patients, post-ASCT maintenance therapy with thalidomide appears to increase tumor burden reduction .
- In 2009 maintenance therapy with thalidomide, lenalidomide, or bortezomib was still of questionable benefit.

Relapse

- The natural history of myeloma is of relapse following treatment. Options for relapsed disease include re-treatment with the original agent, use of other agents , and a second autologous stem cell transplant.

- Later in the course of the disease, "treatment resistance" occurs. This may be a reversible effect, and some new treatment modalities may re-sensitize the tumor to standard therapy. The newly approved thalidomide derivative pomalidomide may be used for relapsed and refractory multiple myeloma.

Associations between clinical manifestations and types of kidney injury in MM

Predominant renal syndrome	Major types of renal lesions
Acute kidney injury (AKI)	Myeloma cast nephropathy Acute tubular necrosis Iatrogenic effects Direct infiltration of renal parenchyma Acute tubulointerstitial nephropathy
Proteinuria/nephrotic syndrome	Monoclonal Ig deposition disease (MIDD) Amyloidosis Rare types of glomerular involvement
Chronic kidney disease (CKD)	Amyloidosis Myeloma cast nephropathy Monoclonal Ig deposition disease (MIDD)
Fanconi syndrome	Proximal tubulopathy

Cast nephropathy

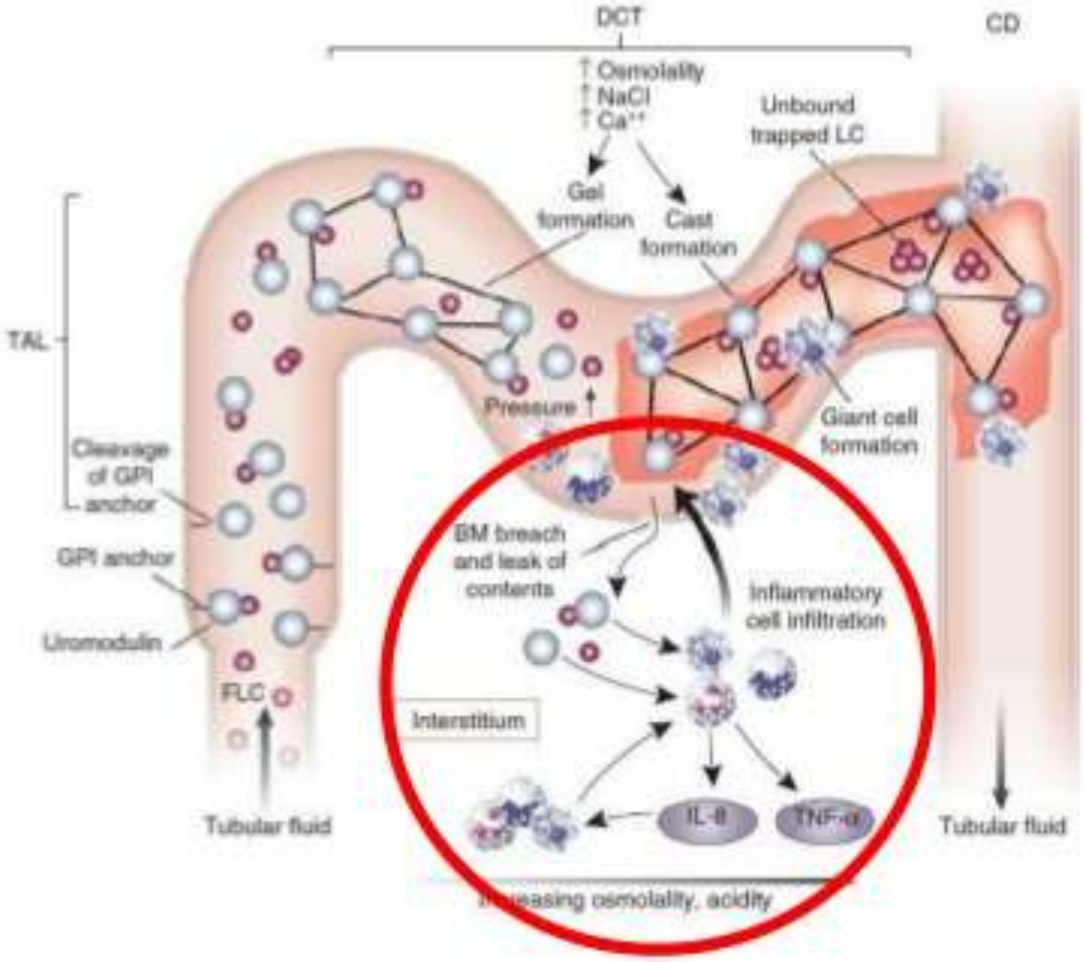
- The term myeloma kidney or myeloma cast nephropathy refers to a disorder in which monoclonal urinary immunoglobulin light chains (Bence Jones proteins) lead to acute or chronic renal failure

Figure 3 | Light chain interactions in the distal nephron.

Fractured **DCT** protein precipitates (casts), consisting of **uromodulin & FLC**

Cast formation is **characteristic** for **Multiple Myeloma.**
But it may also be seen in up to a **third of cases of LCDD**, but is **rare in AL amyloidosis**

Cast is characterized by **tubulointerstitial inflammation and fibrosis**

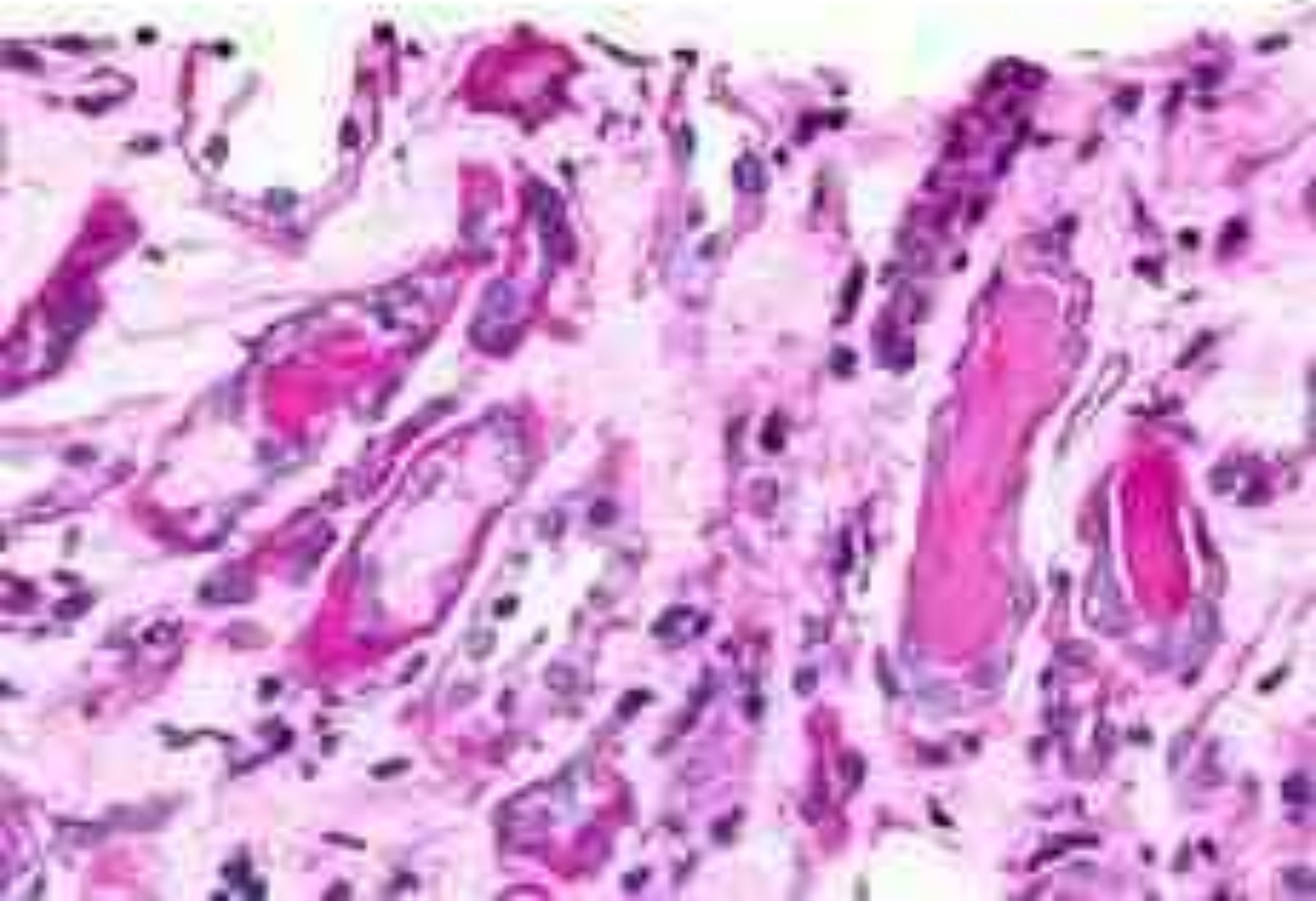


NephroTube

Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301
Pozzi C et al. Am J Kidney Dis 2003; 42: 1154–1163.

Cast nephropathy

- The diagnosis of cast nephropathy is based on the demonstration of tubular casts in the distal nephron that are composed of Ig light chains, and the light chain in the cast is the same as that in the serum and urine.
- The presence of renal disease—renal insufficiency, in particular—in patients with myeloma is of **prognostic** importance because it is associated with a significant increase in morbidity and mortality



Treatment of Cast Nephropathy

- Initial treatment is directed at correcting reversible factors that contribute to reduced GFR and cast precipitation . This includes aggressive hydration (2 to 3 L/d), alkalinization of the urine, discontinuation of NSAID, and avoidance of IV iodinated contrast media .
- Although bisphosphonates are useful in the management of hypercalcemia, they may be associated with ARF and must be used with caution .

Treatment of Cast Nephropathy

- This initial therapy leads to recovery of renal function in up to 50% of cases, often within 1 mo, and is associated with patient survival that is similar to those in patients who have myeloma without renal failure

Treatment of Cast Nephropathy

- In patients who have myeloma and are new to dialysis, successful ASCT has led to recovery of renal function and discontinuation of dialysis in up to 24% of cases . As a result, ASCT is the preferred therapy even in patients with myeloma with advanced renal failure .

Treatment of Cast Nephropathy

- The role of plasmapheresis in the management of cast nephropathy continues to be a topic of considerable debate.

- The recent development of high cutoff (HCO) dialyzers used with extended hemodialysis sessions offers an alternative approach to the efficient removal of SFLC.

Trials

BioMed Central

Study protocol

Open Access

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): A randomised control trial

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Abstract

Background: Renal failure is a frequent complication of multiple myeloma and when severe is associated with a greatly increased morbidity and mortality. The principal cause of severe renal failure is cast nephropathy, a direct consequence of high concentrations of monoclonal free light chains (FLCs) in patients' sera. FLC removal by extended haemodialysis, using a high cut-off dialyser, has recently been described as a novel therapeutic option.

Methods: The **EU**ropean trial of free **LI**ght chain removal by ex**TE**nded haemodialysis in cast nephropathy (EuLITE) trial is a prospective, randomised, multicentre, open label clinical trial to investigate the clinical benefits of FLC removal haemodialysis in patients with cast nephropathy, dialysis dependent acute renal failure and *de novo* multiple myeloma. Recruitment commenced in May 2008. In total, 90 patients will be recruited. Participants will be randomised, centrally, upon enrolment, to either trial chemotherapy and FLC removal haemodialysis or trial chemotherapy and standard high flux haemodialysis. Trial chemotherapy consists of bortezomib, doxorubicin and dexamethasone. FLC removal haemodialysis is undertaken with two Gambro HCO 1100 dialysers in series using an intensive treatment schedule. The primary outcome for the study is independence of dialysis at 3 months. Secondary outcomes are: duration of dialysis, reduction in serum FLC concentrations; myeloma response and survival.

Hypothesis: FLC removal haemodialysis will increase the rate of renal recovery in patients with severe renal failure secondary to cast nephropathy in *de novo* multiple myeloma.

Trial registration: ISRCTN45967602

New strategies

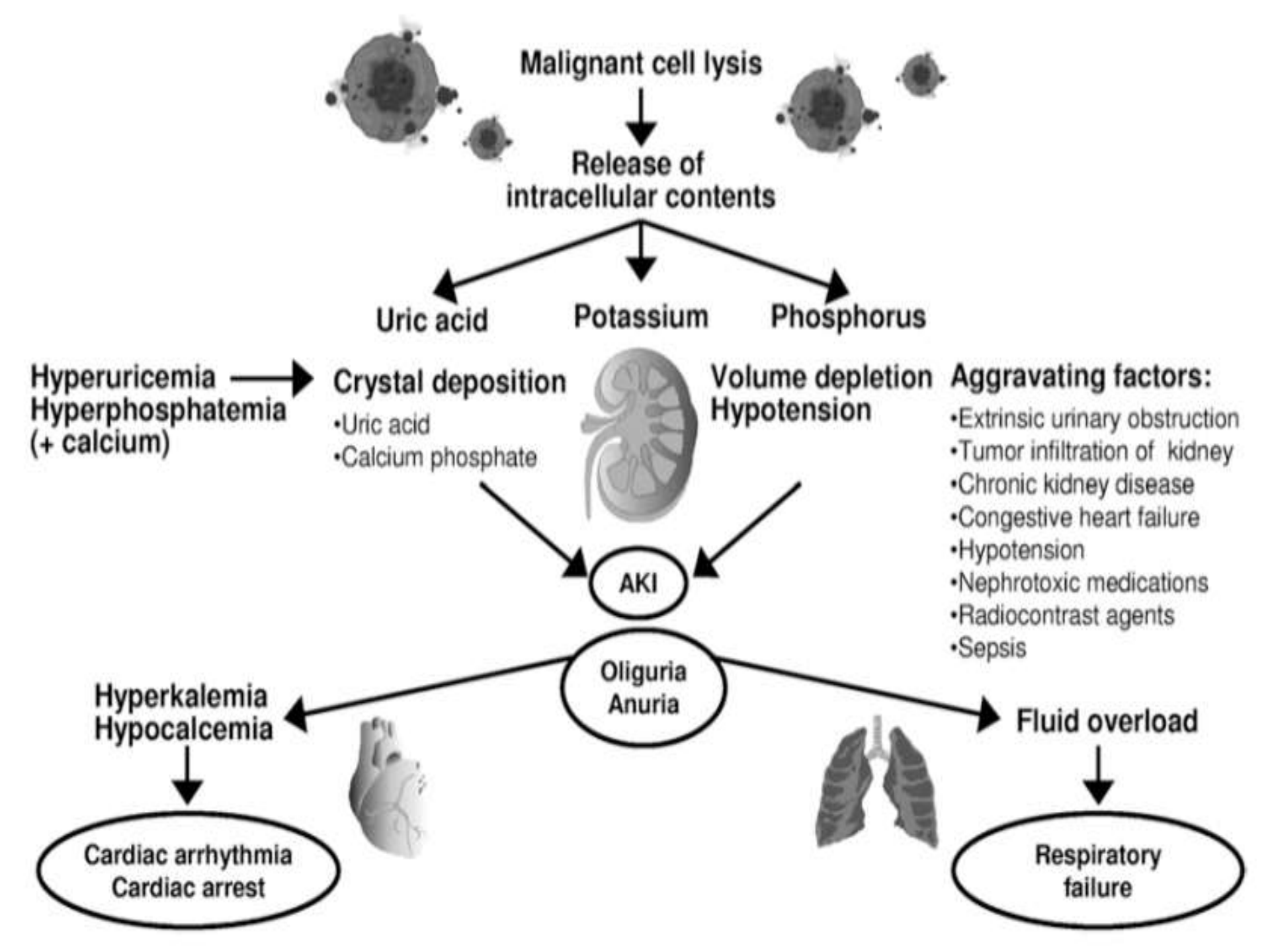
- Pitutary adenylate cyclase activating polypeptide.

- Cyclized competitor peptide.

Prognosis of Cast Nephropathy

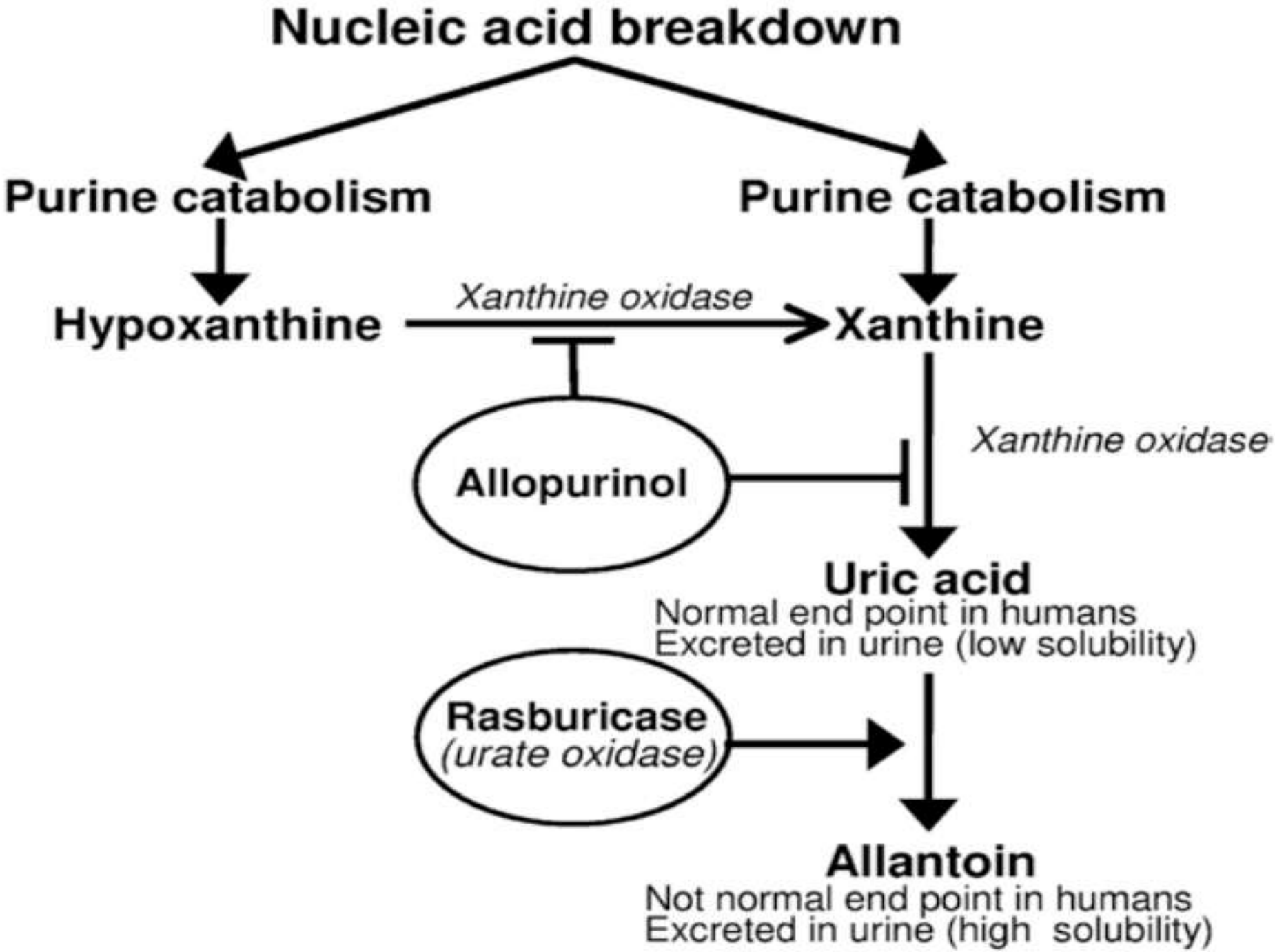
- Even with aggressive treatment, progression to ESRD occurs in up to 65% of patients with cast nephropathy within 3 mo of diagnosis Patients who present with severe or advanced renal failure are most likely to have irreversible disease, with >80% requiring dialysis at presentation and only 15% regaining renal function

Tumor Lysis Syndrome


Malignant cell lysis
Release of intracellular contents
Uric acid
Potassium
Phosphorus
Hyperuricemia
Hyperphosphatemia
(+ calcium)
Crystal deposition
•Uric acid
•Calcium phosphate
Volume depletion
Hypotension
Aggravating factors:
•Extrinsic urinary obstruction
•Tumor infiltration of kidney
•Chronic kidney disease
•Congestive heart failure
•Hypotension
•Nephrotoxic medications
•Radiocontrast agents
•Sepsis
AKI
Oliguria
Anuria
Hyperkalemia
Hypocalcemia
Cardiac arrhythmia
Cardiac arrest
Fluid overload
Respiratory failure

Box 1. Cairo-Bishop Definition of Laboratory and Clinical TLS

- **Serum values included in the definition of laboratory TLS[a]**
  - Uric acid ≥ 8 mg/dL or 25% increase from baseline
  - Potassium ≥ 6 mEq/L or 25% increase from baseline
  - Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
  - Calcium ≤ 7 mg/dL or 25% decrease from baseline
- **Criteria included in the definition of clinical TLS[b]**
  - Serum creatinine ≥ 1.5 value of the upper limit of the age-adjusted normal range
  - Cardiac arrhythmia or sudden death
  - Seizure


Nucleic acid breakdown
Purine catabolism
Purine catabolism
Hypoxanthine
Xanthine oxidase
Xanthine
Allopurinol
Xanthine oxidase
Uric acid
Normal end point in humans
Excreted in urine (low solubility)
Rasburicase
(urate oxidase)
Allantoin
Not normal end point in humans
Excreted in urine (high solubility)

Volume Repletion/Expansion

- Volume depletion can further increase the risk of UA and CaP precipitation.
- Volume repletion/expansion maintains renal blood flow and urine flow, promoting urinary excretion of K, UA, and phosphate.
- Recommended in patients at intermediate and high risk of TLS.
- Recommended that IVF should be started 24-48 hours before chemotherapy at a rate of 80-100 mL/m2/hr in adults to achieve urinary volumes of >3L/d.

Urinary Alkalinization

- Historically, the goal of urinary alkalinization is to maintain urinary pH at 6.5-7.5 to enhance uric acid solubility and excretion.
- Studies in rats have demonstrated that in the absence of increasing urinary flow rates, increasing urinary pH greater than 7.0 was ineffective in preventing UA crystallization.
- Given the lack of demonstrated efficacy and the potential complications of iatrogenic metabolic alkalosis and enhancing CaP precipitation, Heme/Onc guidelines **do NOT recommend** urinary alkalinization in the prevention and treatment of TLS.

Rasburicase

- FDA has approved the use of rasburicase for both the adult and pediatric cancer patients at risk for hyperuricemia.
- Daily cost of a standard dose of rasburicase in a 70 kg patient is approximately **$4400**. (Recommended course is 5 days).

- Recent case series have suggested lower doses with shorter schedules have been equally efficacious as compared to FDA-approved doses.
- Reports suggest that since the introduction of rasburicase, the need for dialysis has “dramatically” declined which may justify rasburicase use from a costeffectiveness standpoint.

Allopurinol vs Rasburicase

- There have been two phase 3 randomized control trials prospectively comparing the efficacy of allopurinol versus rasburicase in hyperuricemia.

- Although both studies showed that addition of rasburicase decreased UA levels more rapidly than allopurinol alone, one study was not powered to find a difference in AKI and dialysis rates, while the other did not report the effect of these therapies on kidney function.

Chemotherapeutic agents and AKI

Commonly Used Treatments in Cancer Patients that May Cause Renal Toxicity

Tubular Injury	Glomerular Injury	Renal Vascular Injury
Acute Tubular Injury	**FSGS**	**Thrombotic Microangiopathy**
Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed	Interferon (IFN), pamidronate, zoledronate	Bevacizumab (anti-VEGF monoclonal antibody)
Tubular Syndromes	**Minimal Change Disease**	**Tyrosine Kinase Inhibitors**
Renal Tubular Acidosis	IFN, pamidronate	Sorafenib, sunitinib, imatinib
Ifosfamide, amphotericin, calcineurin inhibitors	**Proteinuria**	**Other Agents**
Fanconi-like Syndrome	Sorafenib, sunitinib, vatalanib, axitinib	Gemcitabine, mitomycin C, interferon-α (IFN-α)
Cisplatin, ifosfamide, azacitidine, diaziquone, imatinib, pemetrexed		
Salt Wasting		
Cisplatin, azacitidine		
Magnesium Wasting		
Cetuximab, cisplatin, panitumumab		
Nephrogenic Diabetes Insipidus		
Cisplatin, ifosfamide, pemetrexed		
Acute Interstitial Nephritis		
Sorafenib, sunitinib		
Crystal Nephropathy		
Methotrexate, acyclovir		
SIADH		
Cyclophosphamide, vincristine		

Chemotherapeutic Agents

Glomerulus	VEGF inhibitors, Nitrosoureas, Interferons
Tubules	Cisplatin, Carboplatin, Ifosfamide, Cyclophosphamide, Streptozocin, Nitrosoureas, Methotrexate
Interstitium	Cisplatin, Carboplatin
Renal microvasculature	VEGF inhibitors, Mitomycin, Gemcitabine

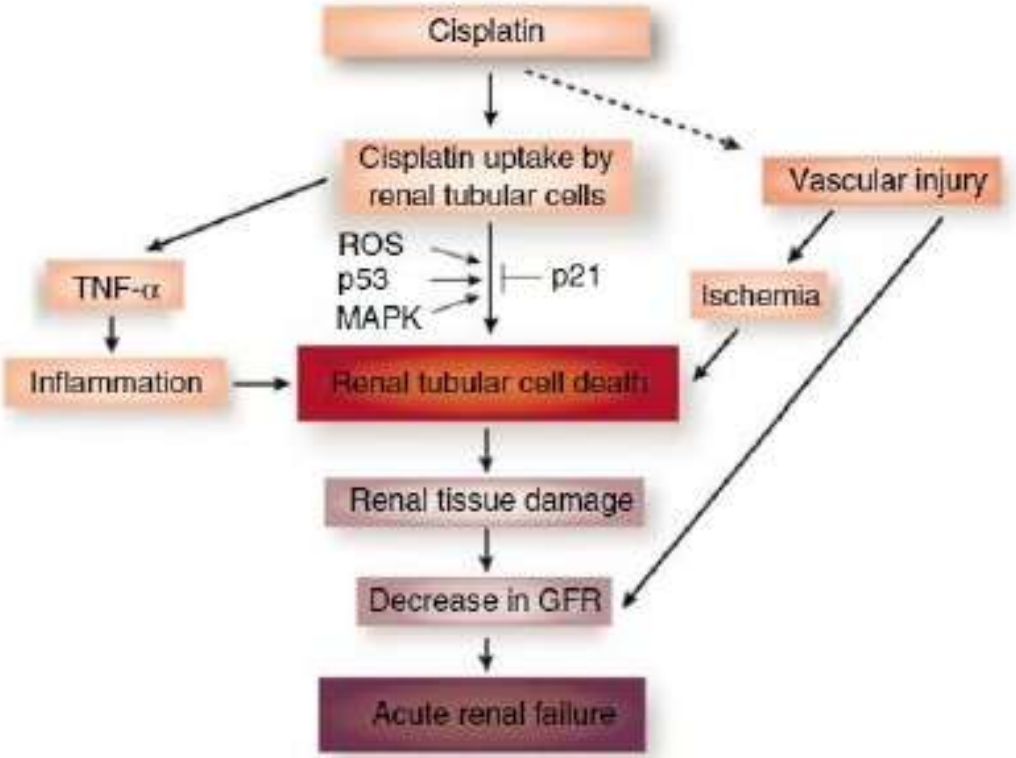


Figure 1 | Overview of the pathophysiological events in cisplatin nephrotoxicity. Cisplatin enters renal cells by passive and/or facilitated mechanisms. Exposure of tubular cells to cisplatin activates signaling pathways that are cell death promoting (MAPK, p53, ROS, and so on) or cytoprotective (p21). Meanwhile, cisplatin induces TNF-α production in tubular cells, which triggers a robust inflammatory response, further contributing to tubular cell injury and death. Cisplatin may also induce injury in renal vasculature, leading to ischemic tubular cell death and decreased glomerular filtration rate (GFR). Together, these pathological events culminate in acute renal failure.

HSCT and AKI

Causes of Acute Kidney Injury (AKI) and Other Renal Disease in Relation to the Timing of Hematopoietic Stem Cell Transplantation (HSCT)

Peri-HSCT	Tumor lysis syndrome from conditioning regimen (rare) Systemic toxicity from conditioning regimen—for example, volume depletion (common) Dimethyl sulfoxide (DMSO)–induced hemolysis, acidosis, and pigment nephropathy (rare)
Days to weeks after HSCT	Pre-renal AKI from volume depletion, AKI from neutropenic sepsis and drug toxicity (common) AKI related to engraftment syndrome (rare)
Weeks to months after HSCT	AKI from sepsis, volume depletion, drug and radiocontrast toxicity (common) AKI from veno-occlusive disease of the liver, graft-versus-host disease (GVHD), thrombotic microangiopathy, and BK virus nephropathy (rare)
Months to years after HSCT	CKD from previous AKI, from continuous use of calcineurin inhibitors especially with GVHD, and from preexisting cancer—for example, myeloma (common)

- The incidence of ARF after autologous HCT is lower than after allogeneic HCT.

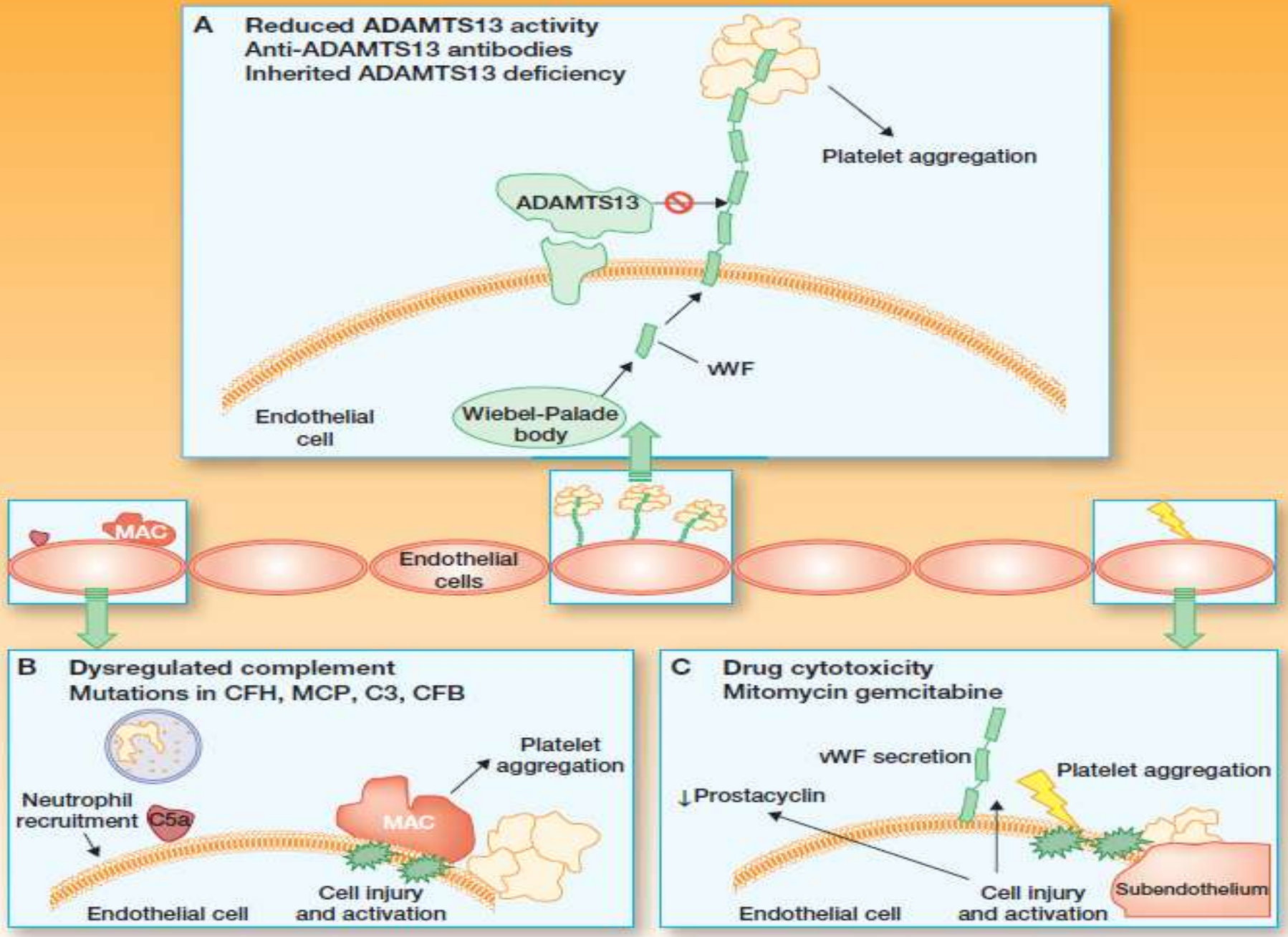
- Lower rates of ARF occur after non myeloablative-HCT compared with myeloablative- HCT.

Thrombotic microangiopathy

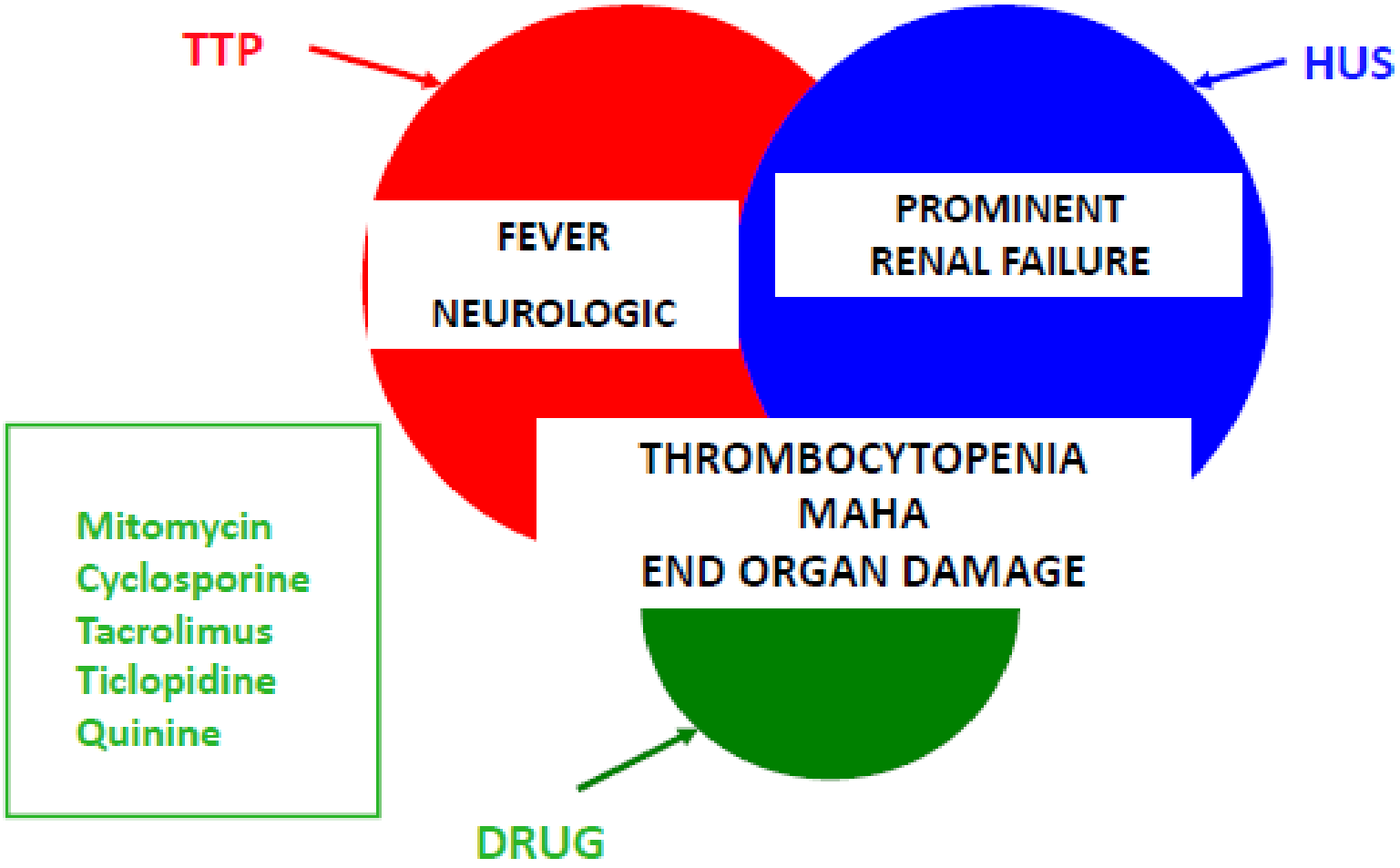
Pathogenesis of TMA is Variable

Pathology	Mechanism	Clinical Disease
Systemic platelet thrombi	Inability to degrade large vWF multimers	TTP
Predominant renal platelet-fibrin rich thrombi	Shiga toxin causing endothelial cell damage	HUS
	Factor H deficiency and complement activation	Atypical HUS
Systemic and renal thrombi	Drugs and stem cell transplant, endothelial damage, malignancy	Features of TTP and HUS

Mayer, Mt Sinai J, 2005



Clinical Overlap



Chemotherapy-Associated TMA

Table 1. Characteristics of TMA associated with mitomycin and gemcitabine

Chemotherapy	Incidence	Clinical presentation	Onset	Prognosis
Mitomycin	2–15%	Severe MAHA; thrombocytopenia; renal dysfunction; elevated lactate dehydrogenase; elevated bilirubin; pulmonary edema	Cumulative doses >30 mg/m^2 and >1 year of treatment	Mortality ~75% related to renal failure
Gemcitabine	0.25–0.4%		2,000–48,000 mg/m^2 and 5–8 months of treatment	Mortality ~60%; renal failure 34–69%; reversal of anemia and thrombocytopenia may be common

Malignancy-associated thrombotic microangiopathy

- ADAMTS13 activity is not significantly reduced
- Plasma exchange has no benefit (Werner et al, 2007). The treatment of the underlying cancer is the mainstay of therapy.

Table 1 Systemic Malignancies Associated With Microangiopathic Hemolytic Anemia and Thrombocytopenia

	Data Sources						
Malignancy	Brain 1962[2] (N = 5)	Antman 1979[5] (N = 55)	Oklahoma 2007[6] (N = 10)	Multiple Reports From the Literature[6] (N = 19)	Oberic 2009[9] (N = 20)	Elliott 2010[10] (N = 7)	Total (N = 65)
Gastric carcinoma	3	30		5	4	1	43
Breast carcinoma		7	2	1	7	4	21
Lung carcinoma	1	4	2	1	3	1	12
Prostate carcinoma	1	2		4	2		9
Carcinoma of unknown origin		5		3	1		9
Colon carcinoma		1		1	1		3
Hepatoma		1			2		3
Pancreatic carcinoma		2	1				3
Anal squamous cell carcinoma				2			2
Non-Hodgkin lymphoma			1	1			2
Acute lymphocytic leukemia			1				1
Cholangiocarcinoma		1					1
Kaposi sarcoma			1				1
Multiple endocrine neoplasia type 1				1			1
Myelodysplastic syndrome			1				1
Neuroendocrine tumor						1	1
Ovarian carcinoma		1					1
Renal carcinoma			1				1
Seminal vesicle tumor		1					1

In the patients reported from the Oklahoma TTP-HUS Registry[6] and the Mayo Clinic,[10] the systemic malignancies were not suspected when plasma exchange treatment for the diagnosis of TTP (thrombotic thrombocytopenic purpura) was begun. Many patients in the other reports had clinically overt and recognized malignancies when the microangiopathic hemolytic anemia and thrombocytopenia occurred. The data from Antman et al[5] include 4 patients whom they reported on and 51 previously reported cases. Patients from the Oklahoma literature review[6] are from a systematic review through January 2006 to identify all previously reported patients[1] in whom TTP or HUS (hemolytic-uremic syndrome) was initially suspected[2] and malignancy was not considered as an initial diagnosis.[3] The patients had not received chemotherapy, nor was there evidence of malignancy within the previous year,[4] and there was no evidence of disseminated intravascular coagulation. None of the patients identified in the Oklahoma[6] review were previously identified in the review by Antman et al.[5]

Bone marrow transplant-associated microangiopathy

- Management is difficult, as stopping CSA or switching to another immunosuppressive, such as tacrolimus, may worsen GVHD.

- No benefit has been shown with Plasma exchange.

THANK YOU